“Studies towards the impurity profiling, forced degradation, analytical method development, validation for various drug formulations used in the treatment of lung diseases”.

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1.0 Introduction of proposed research:

An impurity in a drug substance / drug products as defined as any component of the drug substance / drug products that is not the chemical entity defined as the drug substance / drug products and affects the purity of active ingredient of drug substances / drug products. Hence, any extraneous material present in the drug substance or in the drug product has to be considered an impurity even if it is totally inert or has superior pharmacological properties. Impurities are the unwanted chemicals that remain with active pharmaceutical ingredients (APIs) or drug product formulations. The presence of these unwanted chemicals even in small amounts may influence the quality, efficacy and safety of the pharmaceutical products (1).

Concept about purity changes with time and it is inseparable from the developments in analytical chemistry (3) and day by day increasing interest of Impurity profiling study. The major challenge for both bulk drug and pharmaceutical industries is to produce quality products. It is necessary to conduct vigorous quality control checks in order to maintain the quality and purity of products. Impurity profiling is the common name of a group of analytical activities, for the detection, identification / structure elucidation and quantitative determination of organic, inorganic impurities and residual solvents in bulk drugs and pharmaceutical formulations. Various regulatory authorities such as • The International Council for Harmonisation (ICH) • The United States Food and Drug Administration (USFDA) • The European Medicines Agency (EMA) • The Canadian Drug and Health Agency • The Japanese Pharmaceutical and Medical Devices Agency (PMDA) • The Australian Department of Health and Ageing Therapeutic Goods in addition several official compendia, such as the British Pharmacopoeia (BP), the United States Pharmacopeia (USP), the Japanese Pharmacopoeia (JP), the European Pharmacopoeia (EP), Indian Pharmacopeia (IP) and the Pharmacopoeia of the People's Republic of China (ChP) are focus on the control of impurities and incorporating the very stringent limits on levels of various impurities that restrict the impurity levels present in APIs and drug formulations.

1.1 Impurity profiling for anti-asthma drugs:

When you breathe, your lungs take in oxygen from the air and deliver it to the bloodstream. The cells in your body need oxygen to work and grow. During a normal day, you breathe nearly 25,000 times. People with lung disease have difficulty breathing. Millions of people in the U.S. have lung disease. If all types of lung disease are lumped together, it is the number three killer in the United States. The term lung disease refers to many disorders affecting the

lungs, such as asthma, Chronic obstructive pulmonary disease (COPD), infections like influenza, pneumonia and tuberculosis, lung cancer, and many other breathing problems. Some lung diseases can lead to respiratory failure.

People with obstructive lung disease have shortness of breath due to difficulty exhaling all the air from the lungs. Because of damage to the lungs or narrowing of the airways inside the lungs, exhaled air comes out more slowly than normal. At the end of a full exhalation, an abnormally high amount of air may still linger in the lungs. The most common causes of obstructive lung disease are Chronic obstructive pulmonary disease (COPD) and the Asthma.

Asthma is a lung disease, is a condition in which your airways narrow and swell and may produce extra mucus. This can make breathing difficult and trigger coughing, a whistling sound (wheezing) when you breathe out and shortness of breath. Asthma can start at any age. Moreover, asthma places a huge burden at the societal, financial and health-care levels of nations.

Different drug products are available in the market, such as, Fluticasone (Flovent HFA), Budesonide (Pulmicort Flexhaler), Mometasone (Asmanex Twisthaler), Beclomethasone (Qvar RediHaler), Ciclesonide (Alvesco), Montelukast (Singulair), Zafirlukast (Accolate), Zileuton (Zyflo),Theophylline, Albuterol (ProAir HFA, Ventolin HFA, others), Levalbuterol (Xopenex HFA), Ipratropium, Prednisone, Methylprednisolone etc. Some inhaled asthma medication combinations contain both a corticosteroid and a bronchodilator: Fluticasone and salmeterol (Advair Diskus), Budesonide and formoterol (Symbicort) Mometasone and formoterol (Dulera), Fluticasone and Vilanterol (Breo) etc. Impurity profiling test is mandatory and important for the quality, safety and efficiency of lung diseases bulk drugs and drug product and it is need of time.

2.0 Literature review of the proposed topic:

As per the statistics / Drugbank online survey 2021, more than 14528 total number of drugs present in the world (Drugbank 2021) (8) and as per the Karen Bissell, 2019, “Essential Medicines at the National Level: The Global Asthma Network’s Essential Asthma Medicines Survey 2014, and Karen Bissell, Philippa Ellwood, 2019, “International general of Environmental research and public health,” study estimated that there are 339 million peoples are affected with asthma globally and more than 500 anti-asthma drugs are present in world.

The issue of impurities in medications is complicated and involves aspects of chemistry, biology, drug safety, and analytical power, and also epistemology and ethics, Ahmad Yaman Abdin, Prince Yeboah et al. 6 February 2020, “Chemical Impurities: An

Epistemological Riddle with Serious Side Effects, International journal of Environmental research and public health".

As per Krunal J Prajapati (2018), unidentified and potential toxic impurities are hazardous to health, so in order to increase the safety of drug therapy; impurities should be identified and determined by selective analytical methods, Krunal J Prajapati, Charmy S Kothari in 2018, "Impurity Profile of Bronchodilators used in Asthma: A Critical Review Current Drug Discover Technology, 2018;15(4):272-304. National library of medicine".

By Arun Bhutnar in July 2017, Arun Bhutnar, Sachin Khapare et al. (2017), "Isolation and Characterization of Photodegradation Impurity in Budesonide Drug Product Using LC-MS and NMR Spectroscopy, American Journal of Analytical Chemistry, ISSN Online: 2156-8278, Volume 8, Number 7 , July 2017", different conditions for degradations like hydrolytic (acidic, basic and neutral), oxidative, photolytic, thermolytic and various analytical methods have been discussed in detail.

So many research publications have published in the field of impurity profiling of bulk drugs and drugs formulations has a very broad area of research but still a lot of work to be remaining in this field, as per the Rane Holom in 2015, Impurities will be present in all drug substances and drug products, i.e. nothing is 100% pure if one looks in enough depth, "Rane Holom' David P.Elder 2016, "Analytical advances in pharmaceutical impurity profiling, European journal of pharmaceutical science, volume 87, 25 May 2016, Pages 118-135".

As per the Global asthma report 2014, asthma is defined as a heterogeneous disease usually characterized by chronic airway inflammation (GINA 2016) affecting almost 334 million people worldwide.

As per the P.Venkatesan and K.Valliappan 2015, "Impurity Profiling: Theory and Practice, Journal of Pharmaceutical Sciences and Research, Vol. 6(7), 2014, 254-259," there is an ever increasing interest in impurities present in APIs and drug formulations. Now days, not only purity profile but also impurity profile has become mandatory according to various regulatory authorities and has gained importance in modern pharmaceutical analysis due to the fact that unidentified, potentially toxic impurities are hazardous to health and in order to increase the safety of drug therapy, impurities should be identified and determined by selective methods.

As per the Gupta Raghav, Dr. Jain Suresh et al in 2014, "A Review on the Impurity profile of Pharmaceuticals, International Journal of drug Formulation and Research," Gupta Raghav et al / IJDFR volume 5 Issue 2 Mar-Apr 2014, discussed the Impurity profiling, selective analytical methods and about various regulatory authorities and different pharmacopoeias.

As discussed by Sunny Nagpal, Karan et al. (2014), "A Review on Need and Importance of Impurity Profiling, Journal Name: Current Pharmaceutical Analysis, Volume 7," Impurity profiling is the common name of a group of analytical activities, the aim of which is the detection, identification /structure elucidation and quantitative determination of organic, inorganic and residual impurities.

3.0 Gaps in the existing research work:

Certain major gaps in this subject are as below,

- Little research work has been performed on the impurity profiling work of lung diseases drugs and drugs formulations.
- Qualitative / quantitative related substances tests for many bulk drugs and pharmaceutical formulations are not developed up to this stage, so exact qualification / quantification of impurity not possible.
- Stability indicating methods by forced degradation study not well developed.
- Even after the high level of impurity present in bulk drugs and pharmaceutical formulations, impurity profiling methods not available for certain drugs and drug products.
- Absence of the use of modern analytical techniques for impurity profiling.
- Absence of scientific study and is the need of time so there are broad scope to generate knowledge in this field.

4.0 Statement of proposed problem:

Quality is the most important attribute of any pharmaceutical product. Impurity profiling helps in detection, identification and quantification of various types of impurities and residual solvents in bulk drugs and drugs formulations and has a great significant role in the pharmaceutical field. By using the developed impurity profile methods we can find the amount and the type of various impurities, which are injurious to health with the help of various analytical techniques leads to increase the safety of drug therapy. The present research will be helpful serve the life on the earth and uses in the traditional pharmaceutical practices and ultimately accelerates the pharmaceutical research.

5.0 Scope of research work:

The scope of proposed research work is as below,

- Now a day, for the quality, safety, efficiency of bulk drug and drug products, impurity profiling is mandatory requirement as per various regulatory agencies and various pharmacopoeias.

- It is necessary to develop, validate, Forced degradation / stability indicating related substances method for bulk drugs and drug products.
- This research provides a perspective on impurities in drug substance and drug product.
- Impurity profile of pharmaceuticals is receiving an increasing importance and drug safety receives more and more attention from the public and from the media.
- This research provides the valuable information about the impurity types and various techniques of isolation and characterization, analytical techniques for the determination, qualification / quantification of impurities and critical factors to be considered while preparation of the bulk drugs and formulated products.
- The present study helpful for the registration of new pharmaceuticals in regulatory countries.
- The present study will be helpful serve the life on the earth and uses in the traditional pharmaceutical practices.
- Analytical chemistry plays an important role in drug discovery field and this research increases the weightage of analytical field.
- Present research charge up the research in anti-asthma class drugs ultimately accelerates the pharmaceutical research.

6.0 Relevance of the research work:

Developed research will provides a perspective on impurities in drug substance and drug product. Impurity profile of pharmaceuticals is receiving an increasing importance and drug safety receives more and more attention from the public and from the media. Present study will be helpful serve the life on the earth and uses in the traditional pharmaceutical practices and has great importance for social, local, national and international level.

7.0 Significance of proposed problem:

Impurity profile of pharmaceuticals is receiving an increasing importance and drug safety receives more and more attention from research. Impurity profiling can act as a quality control tool. It can provide crucial data regarding the toxicity, safety, various limits of detection and limits of quantitation for all organic, inorganic and residual impurities, usually accompany with bulk drugs and products.

8.0 Objectives of the proposed research:

- Develop degradation pathways of drug substances and drug products.

- To differentiate degradation products that are related to drug products from those that are generated from non-drug production a formulation.
- Elucidation of the structure of degradation products.
- To determine the intrinsic stability of drug substances and drug products.
- To reveal the degradation mechanisms such as hydrolysis, oxidation, thermolysis or photolysis of the drug substances and drug products.
- Established stability indicating nature of a developed method.
- To understand the chemical properties of drug molecules.
- Generate more stable formulations.

9.0 Hypotheses / Assumptions:

For the anti-asthmatic drugs new method developments & validations of developed methods, effect of certain degradants to develop the degradation products, separation, identification and quantification of known and unknown observed impurities and degradant by using the modern analytical techniques (Techniques to be used are described in point 10.e.).

10.0 Research Methodology:

10.a. Methods of research

Different conditions for degradations like thermolytic, photolytic, heat, humidity, acidic, basic, neutral, oxidative, have to be used. Furthermore, explained the name along with number of impurities and degradants present in different drugs. The name as well as structures of all the observed impurities in different drugs will included, which can aid in impurity profiling. Various analytical methods, including Chromatographic techniques and Spectroscopic techniques to be used for the identification and quantification of impurities. Laboratory analytical methodology to be used in this research, this research related to pure qualitative and quantitative analysis.

10.b. Sampling design

The sampling goal is to collect samples that provide an accurate representation of the Impurity profiling.

10.c. Methods of data collection

The data will be collected by the electronic media available with the modern analytical techniques.

10.d. Methods of data analysis

Data analysis will be performed by applying systematic statistical and /or logical techniques. To describe and illustrate, condense and recap, the data will be evaluated.

10.e. Details of equipment's and instruments to be used and their source

Analytical instruments such as, high performance liquid chromatography (HPLC), Gas chromatography (GC), Thin layer chromatography (TLC), UV spectroscopy, IR spectroscopy Liquid Chromatography (LC)-Mass Spectroscopy (MS), LCNMR, LC-NMR-MS, GC-MS, and LC-MS, Gas–liquid chromatography, Gravimetric analysis, Solid-phase extraction methods, Liquid–liquid extraction method, Mass spectrometry, Nuclear magnetic resonance (NMR) spectroscopy, and RAMAN spectroscopy are to be used in research.

11.0 Chapter Scheme:

Tentative chapterization as follows,

Chapter 1 Introduction

Chapter 2 Review of Literature

Chapter 3 Information related to the selected drugs and drug products. Materials and Methodology

Chapter 4 Method developments for the Impurity Extraction, Isolation, separation from various anti-asthmatic bulk drugs and drug product by using modern analytical techniques.

Chapter 5 Stability studies and Forced degradation treatments means the effects of cumulative concentrations of Temperature, Heat, Light, Humidity, Acids, base, Peroxide and other degradants.

Chapter 7 Characterization of observed impurities and degradation products present in anti-asthmatic bulk drugs and drug product by using modern analytical techniques.

Chapter 8 Validations of the newly developed Impurity profiling methods.

Chapter 9 Complete impurity profiling guidance such as classification and identification of impurities, report generation, listing of impurities in specifications and a brief discussion.

12.0 Expected outcome:

Impurities in new drug substances and products are addressed from two perspectives such as c*hemistry aspects* and s*afety aspects*:

In short the expected outcome from the proposal is as below,

- Impurity profiling provides the valuable information about the impurities types and various techniques of isolation and characterization, analytical techniques.
- The study helpful for the registration of new pharmaceuticals in regulatory countries.

- This study increases the weightage of analytical chemistry.
- This study charge up the research in antiasthma class drugs ultimately accelerates the pharmaceutical research.
- The study will be helpful serve the life on the earth and important in the traditional pharmaceutical practices.
- Ultimately the outcome of the study important to human being.

13.0 Plan of work (Time schedule of activity):

Sr. no.	Activity	Time (Month)
1	Literature survey,	4month
2	Selection of drugs and drug formulations.	4 month
3	Submission of work progress report	
4	Total time for completion of practical work in lab (Method development and method validations for all selected drugs and drug formulation)	8 months
	Submission of work progress report	
5	a) Data collection, inputs of research guide and finalization of analyzed data. b) Manuscript writing and publication	6 months
6	Final synopsis and Progress report submission.	
	Thesis writing under the guidance of research guide	4 months
7	Completion of remaining work	4months
8	Thesis submission & completion	6 months
Total time		36 months

Time required to complete the present research is not more than 36 months (3 years).

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